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(see editorial "Antibiotic Standards U. S. P. or F. D. A.?")

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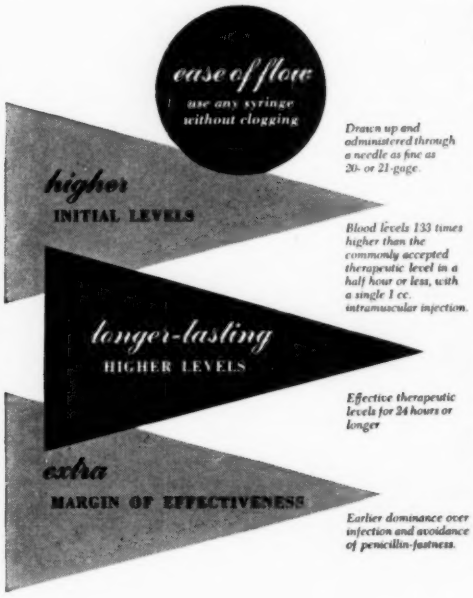
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E D I T O R I A L

ANTIBIOTIC STANDARDS U. S. P. or F. D. A.?

PROPOSED legislation granting the Food and Drug Administration the authority to certify the potency and purity of all antibiotics is another step in the direction of centralized control of the drug industry.

When the law was passed several years ago giving such power to the F. D. A. with respect to penicillin we were entering a new drug field about which little was known and we were at war. These circumstances then to many made rigid governmental certification seem a logical step, although strong arguments could be and were entered against it. At the present time there is every reason why even the certification of penicillin should be abandoned rather than to expand the powers of the F. D. A. to cover other antibiotics.

For many years we have had in the United States Pharmacopoeia and the National Formulary a means of establishing legal standards for the purity and strength of drugs. Generally speaking, this system has worked well and it continues to do so. It is difficult, if not impossible, to offer a valid argument for treating penicillin or any other antibiotic differently than dozens of other potent drugs now simply controlled by means of an official monograph. Are not digitoxin, ouabain, thiopental sodium and many others just as hazardous if impure or below strength as penicillin? No special case can be made for penicillin at the present time and yet the U. S. P. is forced to state "It complies with the requirements of the Federal Food and Drug Administration," in other words, a superior authority.

The truth is that penicillin is so devoid of toxicity that it may be used in unlimited doses without untoward effects except an occasional allergic reaction which cannot be prevented by a control measure on the drug itself. Why then does penicillin need certification? In what way is it a special case?

It is the writer's opinion that too many persons in industry and in charge of Pharmacopoeial policy fail to protect both industry and

others against the continued encroachment on what should be the prerogative of the *United States Pharmacopoeia*. The mere fact that government officials propose and advocate a system circumventing our present control by the democratic process of Pharmacopoeial standardization is not a sufficient reason for fear and trembling lest certain government officials be offended. This is still a democracy, at least in part, and the wishes of these officials should be of no greater significance than those of the many others outside the government who are concerned with drug standardization and control. It would almost seem that some persons are inclined to "go along" on many of these government proposals, rather than oppose them, in the hope of gaining some special favor along other lines. If such is the case how little do they know and understand the fallacy of appeasement! How little do they perceive the end result of such a policy!

If by slow degrees we are not to lose in this country the unique but outstanding system that we now have, a system of setting our own standards for drugs by democratic procedure, we must oppose the special treatment given certain drugs unless it be recognized definitely only as a transitional measure. If the F. D. A. wishes to control drugs pending the adoption of official standards there should be no objection. On the other hand we should insist that once recognition is given in the U. S. P. or N. F. these standards and these only shall be binding upon the manufacturer. Nothing must be allowed to take precedence over the official compendia and their standards. If we default on this essential point then the *United States Pharmacopoeia* and the *National Formulary* may become only a rubber stamp of approval for governmental dictum.

It is an inescapable fact that government agencies by their very nature tend to acquire more power and with it more personnel. This is the history of government everywhere and it is not peculiar to our own Food and Drug Administration. We do not impugn the motives of the Food and Drug Administration. A desire to grow in power and influence is a universal human trait. Industry is checked in its tendency to concentrate its power by anti-trust laws but what controls the growth of government? This natural trend in government must be recognized and our independent institutions protected against absorption and assimilation.

Throughout the years many men have served without pay and at great personal sacrifice to maintain both the U. S. P. and the N. F. as outstanding examples of what can be accomplished by free men in setting standards for the protection of the public health and welfare. It has not been established that they have failed in this purpose and we are opposed to any means of "super" control which transcends the official compendia in establishing standards for drugs in the United States.

L. F. Tice

THE CHEMICAL MICROSCOPY OF ESSENTIAL OILS. V. REACTION OF CATNIP OIL WITH PHENYLHYDRAZINE.

By L. Wilson Greene *

THE leaves and flowering tops of the catnip herb (*Nepeta cataria*, Linné, Fam. *Labiatae*) yield approximately 0.3% of a volatile oil on distillation with steam. The herb is also known as catnep, catmint, and a cat's wort. This perennial plant is indigenous to Asia and Europe and has been naturalized in the United States.

The early chemistry of catnip oil is obscure. Umney and Bennett (1) examined a sample of Sicilian oil and reported that it had a total alcohol content of 22.2% (as menthol) and an ester content of 3.3% (as menthyl acetate). The possible presence of a small amount of a ketone, either menthone or pulegone, was suggested by these investigators. Hixon (2) was under the impression that the oil contained a dicyclic sesquiterpene. In Russia, Rutovski and Vinogradova (3) reviewed all previous work on the composition of catnip oil and concluded that it had an aldehyde content of 30%, and that the oil was composed of α- and β-citral, limonene, dipentene, geraniol, citronellol, nerol, a laevorotatory sesquiterpene, acetic acid, butyric acid, and valeric acid.

More recent work shows that these reported findings are in error. Kremers (4) observed the presence of an acidic constituent in the oil and this acid was investigated by Meyer (5), working under Kremers' supervision. McElvain and coworkers (6) continued the investigation on the composition of catnip oil and found that the acidic constituent was mainly nepetalic acid, with small amounts of other acids present. To these they gave the names nepetonic acid, nepetic acid, and nepetalinic acid. The McElvain team found that about half of the oil is composed of nepetalactone and about a third is nepetalic acid. The remainder is mostly β-caryophyllene and nepetalic anhydride.

Since phenylhydrazine is known to give crystalline reaction products with a number of compounds containing a CO group, the reaction described in the present communication is probably the re-

* Army Chemical Center, Maryland.

sult of a combination between phenylhydrazine and nepetalactone. This was first reported by the author in 1939 (*7*), and since that time there has been an opportunity to study it further and to evaluate the reaction with respect to the entire study of essential oil microscopy. No other publications on the chemical microscopy of catnip oil have been found in the literature.

Experimental

Only one specimen of the oil (No. E-70) was available for study. This was distilled from the flowering herb in July 1929, the plant having been grown at Saratoga, New York. The sample was presented to the author by the Bureau of Plant Industry, U. S. Department of Agriculture, in March 1938, and the experiments reported here were begun in that year.

A drop of the oil (about 2 mm. in diameter) was placed on a glass microscope slide, and a drop of phenylhydrazine (Eastman Kodak Co. product, m. p. 19-19.5 degrees) of about equal size was intimately mixed with it. Small glass rods were employed in handling and mixing the sample and reagent. The preparation was covered with a glass slip and examined under the microscope in ordinary and in polarized light.

In less than five minutes, the preparation became hazy and birefringent crystals, like those shown in Figure 1, were observed at a magnification of 100 diameters. In 15 minutes the preparation was filled with crystals as in Figure 2. These were birefringent

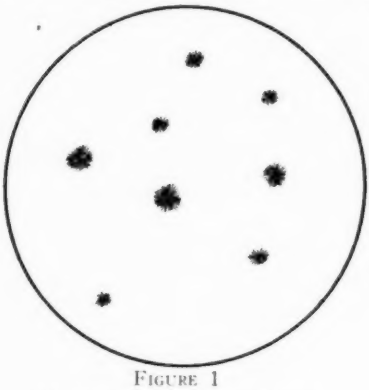

FIGURE 1
APPEARANCE OF PREPARATION AFTER FIVE MINUTES

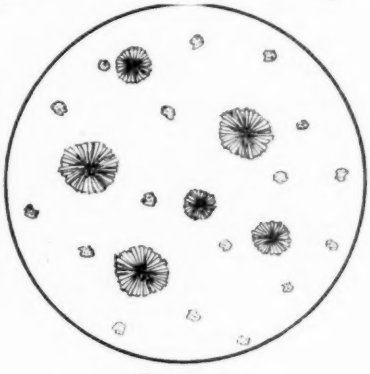

FIGURE 2
APPEARANCE OF PREPARATION AFTER FIFTEEN MINUTES

but showed no interference colors. The next morning the crystals had a more branching structure but no further change was observed after the preparation had stood at room temperature for two days.

This reaction was not given by any of the following essential oils (when the botanical name is given it denotes that the specimen of oil was obtained from a botanically identified source); *Aframomum mala*, ajowan, angelica, anise, asafoetida, bayberry (*Myrica cerifera*), bay (*Myrica acris*), bergamot, bergamot mint (*Mentha citrata*), bitter almond, buchu, cade, calamus, camphor (*Cinnamomum camphora*), Canada snakeroot, cananga, caraway, cardamom, cascarilla, cassia, cedar (*Juniperus virginiana* and *Sabina monosperma*), cedarwood, East African cedarwood (*Juniperus procera*), celery, chamomile (*Anthemis nobilis*), *Chrysothamus nauseosus*, cinnamon bark, cinnamon leaf, citron, citronella, clary sage (*Salvia sclarea*), clove bud, copaiba, coriander, cubeb, cumin, cypress, dill herb, dill seed, dog fennel, elemi, erigeron (*Erigeron canadensis*), eucalyptus (*Eucalyptus citriodora*, *E. globulus*, and *E. staigeriana*), fennel (sweet), galbanum, geranium (*Pelargonium capitatum*), ginger, gingergrass, golden rod (*Solidago canadensis*), grapefruit, guaiacwood, gum plant (*Grindelia squarrosa*), gurjun, hemlock, hops (*Humulus lupulus*), horsemint (*Monarda punctata*), jasmine, juniper, Utah juniper (*Juniperus utahensis*), lavender (*Lavandula latifolia* hybrid, *L. officinalis*, and *L. stoechas*), lavendar (synthetic), lemon, lemongrass (*Cymbopogon citratus*), lime (*Citrus medica*), lovage, mace, mandarin, milfoil (*Achillea millifolium*), mountain laurel (*Umbellularia californica*), mustard (true and synthetic), myrtle, niaouli (*Citrus sinensis*), nutmeg (*Myristica fragrans*), *Ocimum canum*, olibanum, opopanax, orange (natural and terpeneless), origanum, orris root (*Iris florentina*), palmarosa (East Indian geranium—*Cymbopogon martini*), parsley (*Carum piperascens*), patchouly (*Pogostemon patchouli*), pennyroyal, pepper (black), peppermint (*Mentha piperata* and *M. arvensis* var. *piperascens*), perilla leaf (*Perilla ocymoides*), petitgrain (*Citrus aurantium*), pimento berry, pimento leaf, pine, pine needle (*Pinus pumilionis* and *P. sylvestris*), *Pycnanthemum albescens*, pyrethrum (*Chrysanthemum cinerariaefolium*), ragweed (*Ambrosia artemisiaefolium*), red thyme, rose (*Rosa centifolia*), rose geranium (*Pelargonium odoratissimum*), rosemary, rosewood (bois de rose and bois de Siam), rue (*Ruta graveolens*), sage-brush (*Artemisia tridentata*), sandal-

wood, sassafras (true and synthetic), savin, serpolet, snake weed (*Gutierrezia microcephala*), spearmint (*Mentha viridis*), spike lavender (*Lavandula spica*), spruce, star anise, storax (styrax), summer savory (*Saturcia hortensis*), sweet basil (*Ocimum basilicum*), sweet birch (*Betula lenta*), sweet marjoram (*Origanum marjorana*), tagetes (*Tagetes minuta*), tansy (*Tanacetum vulgare*), thuja (*Thuja occidentalis*), thyme (*Thymus vulgaris*), ti-tree (*Leptospermum citrata*), valerian, verbena, vetivert (*Vetiveria zizanioides*), violet (synthetic), wintergreen (*Gaultheria procumbens*), wintergreen (synthetic), wormseed (*Chenopodium anthelminticum*), wormwood (*Artemisia annua*), and ylangylang (*Cananga odorata*).

The following aromatic chemicals did not give the crystalline reaction product typical of catnip oil with phenylhydrazine: carvacrol, carvene (*d*-limonene), carvone, eucalyptol, eugenol, hydroxycitronellol, ionone, linalyl acetate, phenyl acetaldehyde, and terpineol.

Conclusion

The reaction described here, requiring only a very small quantity of sample, appears to furnish a means for establishing the identity of catnip oil, at least for differentiating it from the oils and aromatic chemicals listed above. The test, however, should be confirmed with experiments on other specimens of this oil.

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FREE HALOGENS
A COMPARATIVE STUDY OF THEIR EFFICIENCIES AS BACTERICIDAL AGENTS*

By Louis Gershenfeld, D. Sc., and Bernard Witlin, D. Sc.

ONLY few comparative antibacterial efficiency studies of the free halogens have been reported in the literature (1) (2) (3).

For the most part workers have studied the free halogens separately and have issued individual reports on their respective efficiencies. The technics involved were varied and are difficult to evaluate for comparative purposes.

This research was conducted to obtain findings as to antibacterial efficiencies when testing the free halogens (chlorine, bromine and iodine) in various concentrations under identical conditions. The results thus obtained could be employed for comparative evaluation.

Experimental

Solutions of the halogens under test were prepared as follows:

Chlorine

An aqueous sodium hypochlorite solution (5 percent available chlorine) was employed as the stock solution from which chlorine solutions were prepared.

Bromine

(a) A solution of bromine and potassium bromide in distilled water, the so-called Smith's Bromine Solution N. F. IV (4), was prepared as follows:

To 12.5 grams of potassium bromide dissolved in 80 cc. of distilled water, 8.3 cc. of liquid bromine were added. The mixture was shaken until solution was effected and then made up to a total volume

* This investigation was conducted at the Philadelphia College of Pharmacy and Science, under a grant from the Iodine Educational Bureau's Fellowship at Mellon Institute. Presented before the Laboratory Section of The American Public Health Association at the 76th annual meeting held in Boston, Mass., on November 10, 1948.

of 100 cc. with distilled water. The solution was stored in a brown, glass-stoppered bottle in a dark place.

Chemical analyses (5) were performed to determine the bromine content. An assay made after preparation of the solution revealed 25.1% free bromine. An assay made 18 days later revealed 21.8% free bromine, a loss of 3.3% bromine.

(b) Liquid bromine was dissolved separately in distilled water, McIlvaine's buffer solution (6), Sorensen's buffer solution (6) and aqueous sodium hydroxide by shaking in glass-stoppered bottles until solution was effected.

Iodine

(a) Iodine Tincture containing sodium iodide was prepared in accordance with the U. S. P. XIII (7):

Two grams of iodine and 2.4 grams of sodium iodide were dissolved and made up to 100 cc. with diluted alcohol U. S. P. The final alcohol content was 46%.

(b) Iodine Solution (N. F. VIII) with sodium iodide was prepared as follows: 2 grams of iodine and 2.4 grams of sodium iodide were dissolved and made up to 100 cc. with distilled water.

Tests for Halogens

Tests for the presence of the free halogens were performed immediately preceding and following the bactericidal efficiency tests.

Free chlorine was detected by the use of ortho-tolidine dihydrochloride (8) and by the use of acidified potassium-iodide starch solution (9).

The presence of free bromine was determined by the addition of an excess of potassium iodide to the bromine solution, and the presence of the liberated free iodine was detected by the use of starch test solution U. S. P. (7).

Tests for the presence of free iodine were performed by the addition of starch test solution U. S. P. (7).

Bactericidal Efficiency Tests

One cc. quantities of the halogen solutions respectively were added to varying quantities of 24 hour-old cultures of *S. aureus*,

S. (E.) typhosa, P. aeruginosa, E. coli, B. megatherium (vegetative), *B. mesentericus* (vegetative) and *B. subtilis* (vegetative) at 37°C (4). Sterile F. D. A. broth (10) was used as a control for each series of tests. Transplants (4 mm. loopfuls) were made into 10 cc. quantities of sterile F. D. A. broth at 1, 5, 10 and 15 minute intervals.

Findings

Chlorine

Five cc. of 2 percent available chlorine solutions prepared from sodium hypochlorite displayed bactericidal efficiency against 6 cc. of a 24 hour-old culture of *S. aureus* in 1 minute; 7 cc. of *S. aureus* in 3 minutes; 9 cc. of *S. aureus* in 5 minutes and 10 cc. of *S. aureus* in 15 minutes.

Free chlorine, as noted by employing acidified potassium iodide-starch indicator solution and ortho-tolidine dihydrochloride, was present in mixtures of 5 cc. of 2 percent available chlorine with 5 cc. of 24 hour-old cultures of *S. aureus* before the test, but only in the presence of 1 cc. of *S. aureus* after the test.

The above experiment was repeated employing 1 cc. of 2 percent available chlorine instead of 5 cc. quantities.

One cc. of 2 percent available chlorine displayed bactericidal efficiency against 1 cc. of *S. aureus* in 1 minute; 2 cc. of S. *aureus* in 10 minutes and 3 cc. of *S. aureus* in 15 minutes.

Free chlorine was present in mixtures of 1 cc. of 2 percent available chlorine solution and 1 cc. of a 24 hour-old culture of *S. aureus* before the test, but not at the end of the 15 minute period.

One cc. of 2 percent available chlorine was effective against 15 cc. of 24 hour-old cultures of *S. (E.) typhosa, E. coli* and *P. aeruginosa* within 1 minute, but was ineffective against 1 cc. of 24 hour-old-cultures of *B. mesentericus* (vegetative forms), *B. megatherium* (vegetative forms) and *B. subtiiis* (vegetative forms).

Bromine

(a) Smith's Bromine Solution (21.8 percent free bromine (weight in volume)) in 1 cc. quantities was effective within 1 minute against 40 cc. of 24 hour-old cultures of the test bacteria as follows: within 10 minutes against 50 cc. *S. aureus;* within 1 minute against 60 cc. *S. (E.) typhosa*, 20 cc. *P. aeruginosa*, 60 cc. *E. coli*, 20 cc. *B. subtilis* (vegetative forms), 20 cc. *B. mega-*

therium (vegetative forms) and 20 cc. *B. mesentericus* (vegetative forms); and within 15 minutes against 24 hour-old cultures of *S. aureus, S. (E.) typhosa, P. aeruginosa, E. coli, B. mesentericus* (vegetative forms), *B. megatherium* (vegetative forms) and *B. subtilis* (vegetative forms).

(b) Five cc. bromine 1:1000 (weight in volume) were effective against 0.5 cc. of 24 hour-old cultures of *S. aureus, S. (E.) typhosa E. coli* and *P. aeruginosa* within 1 minute. Five cc. of bromine 1:1000 (weight in volume) were ineffective against 0.5 cc. of 24 hour-old cultures of *B. subtilis* (vegetative forms), *B. megatherium* (vegetative forms) and *B. mesentericus* (vegetative forms).

One cc. of bromine 1:1000 (weight in volume) was inactivated by 0.2 cc. sterile F. D. A. broth.

Five cc. of a concentration of bromine 1:4000 (liquid bromine in water—volume in volume) were effective against 0.5 cc. of 24 hour-old cultures of *S. aureus, S. (E.) typhosa, E. coli* and *P. aeruginosa* within 1 minute.

Five cc. of aqueous bromine solution 1:2000 (volume in volume) were effective against 0.5 cc. of 24 hour-old cultures of *B. subtilis* (vegetative forms), *B. megatherium* (vegetative forms) and *B. mesentericus* (vegetative forms), within 1 minute.

One cc. of 1:1000 bromine (volume in volume) was inactivated by 5 cc. of sterile F. D. A. broth.

Two percent bromine (Smith's Bromine Solution diluted to a 2 percent free bromine concentration with distilled water) in 1 cc. quantities was effective within 1 minute at 37°C. against the following amounts of 24 hour-old broth cultures: 3 cc. of *S. (E.) typhosa*, 3 cc. of *E. coli*, and 1 cc. of *P. aeruginosa*. Two percent bromine in 1 cc. quantities were effective within 5 minutes against 1 cc. of a 24 hour-old culture of *B. mesentericus* (vegetative).

One cc. of two percent bromine was without effect against 1 cc. of 24 hour-old cultures of *S. aureus, B. megatherium* (vegetative) and *B. subtilis* (vegetative) within 15 minutes.

One cc. of 2 percent free bromine solution was inactivated by 7 cc. of sterile F. D. A. broth.

Iodine

Two percent free iodine solutions were effective within 1 minute against the following amounts of 24 hour-old broth cultures: 20 cc.

of *S. aureus*, *S.* (*E.*) *typhosa*, *E. coli*, and *P. aeruginosa*. Ten cc. of 24 hour-old cultures of *B. mesentericus* (vegetative) and *B. megatherium* (vegetative) and 2 cc. of *B. subtilis* (vegetative) were killed in 1 minute.

One cc. of 2 percent iodine was inactivated by 40 cc. of sterile F. D. A. broth.

The Effect of pH

Two percent solutions of the free halogens were prepared in McIlvaine's [1] buffer solutions (6), at pH values varying between 2.2 and 8.0. These were tested for bactericidal efficiency by the Gershenfeld and Patterson technic (11) at 37°C. Higher pH ranges (pH 9.0 to 11.0) for iodine were obtained by the addition of sodium hydroxide to the aqueous solutions. Readings were made with a Beckman electric potentiometer employing sealed glass electrodes.

Chlorine

Solutions containing 2 percent chlorine (as available chlorine prepared from sodium hypochlorite solution) were prepared in McIlvaine's buffer solution at pH 2.2, 3.0, 4.0, 5.0, 6.0, 7.0, and 8.0.

Bactericidal efficiency tests revealed that one cc. of 2 percent chlorine was capable of killing five cc. of 24 hour-old cultures of *S. aureus* at 37°C. within 1 minute when prepared in McIlvaine's buffer solutions at pH 2.2, 3.0 and 4.0, but was ineffective against 5 cc. of 24 hour-old cultures of *S. aureus* at 37°C. within 15 minutes at pH 5.0, 6.0, 7.0, and 8.0.

Bromine

Solutions containing 2 percent free bromine were prepared in McIlvaine's buffer solutions at pH 2.2, 3.0, 4.0, 5.0, 6.0, 7.0 and 8.0. Bactericidal efficiency tests revealed that one cc. of 2 percent free bromine solutions prepared at pH 5.0, 6.0, 7.0 and 8.0 rapidly became turbid and decomposed.[2] One cc. of these solutions prepared at pH 2.2, 3.0 and 4.0 did not reveal bactericidal efficiency against one cc. of 24 hour-old cultures of *S. aureus*.

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[1] McIlvaine's buffer solution, consists of citric acid and dibasic sodium phosphate.

[2] Bromine reacts with citric acid in basic medium to form pentabromoacetone.

Iodine

Solutions containing 2 percent free iodine were prepared at pH 2.2, 3.0, 4.0, 5.0, 6.0, 7.0 and 8.0 using McIlvaine's buffer to obtain the desired pH value. The bactericidal efficiencies of the solutions prepared in McIlvaine's buffer at pH 2.2 and 3.0 were identical with both Iodine Solution (2%) N. F. VIII and Iodine Tincture U. S. P. XIII. However, a decrease in the bactericidal efficiency of the solutions prepared in McIlvaine's buffer was noted as the pH values of the solutions were increased.

Employing normal sodium hydroxide in distilled water as the vehicle, two percent iodine solutions prepared at pH 8.0 displayed greater bactericidal efficiency than Iodine Solution N. F. VIII (12). An increase in pH with sodium hydroxide resulted in a decrease in the bactericidal efficiency of the iodine solutions above pH 8.0.

One cc. of 2 per cent iodine solution prepared in McIlvaine's buffer solution killed 25 cc. of 24 hour-old cultures of *S. aureus* at 37°C. within 1 minute at pH 2.2 and 3.0; 20 cc. of 24 hour-old cultures of *S. aureus* at pH 4.0 and 5.0; 15 cc. of 24 hour-old cultures of *S. aureus* at pH 6.0, 7.0 and 8.0. One cc. of 2 percent iodine prepared in sodium hydroxide, within one minute at 37°C., killed 30 cc. of 24 hour-old cultures of *S. aureus* at pH 8.0, 20 cc. of *S. aureus* at pH 9.0 and 15 cc. of *S. aureus* at pH 10.0; but at pH 11.0 did not kill 15 cc. of *S. aureus* within 15 minutes at 37°C.

The Effect of Buffering Agents

A study was made of the pH changes of 1 cc. of solutions of the free halogens (prepared in McIlvaine's buffer solutions and/or, Sørensen's buffer solutions and/or sodium hydroxide) in combination with 100 cc. of sterile F. D. A. broth or 24 hour-old cultures of *S. aureus* in F. D. A. broth at room temperature (24°C). pH measurements were made with a Beckman electric potentiometer using a sealed glass electrode. Color changes in 100 cc. of the halogen solution, due to pH changes, were also noted upon the addition of normal sodium hydroxide solution.

Chlorine

The sodium hypochlorite solution diluted to 2 percent available chlorine content in McIlvaine's buffer solutions or Sørensen's buffer

solutions (6) at varying pH values did not display buffering action in the presence of sterile F. D. A. broth or 24 hour-old cultures of *S. aureus* in F. D. A. broth.

Color changes in chlorine solutions were not observable due to the virtual lack of color in 2 percent concentrations of available chlorine.

Bromine

Solutions of free bromine buffered with McIlvaine's buffer solutions developed turbidity though some of the mixtures eventually cleared.[3] There was no buffering action evident in the bromine solution in the presence of sterile F. D. A. broth or 24 hour-old cultures of *S. aureus* in F. D. A. broth. Solutions of bromine prepared in Sörensen's buffer solutions remained clear but likewise did not display buffering action. Color changes in the bromine solution occurred first at pH 7.4 (8 cc. of N/1 sodium hydroxide to 100 cc. of 2 per cent aqueous bromine weight in volume) and the maximum color change occurred at pH 8.4 (16 cc. of N/1 sodium hydroxide to 100 cc. of 2 per cent aqueous bromine in weight in volume).

Iodine

There appeared to be a buffering action in the 2 per cent free iodine solutions at the pH range of 6.0 to 7.2 with sterile F. D. A. broth and with 24 hour-old cultures of *S. aureus* in F. D. A. broth. As a control 2.4 per cent sodium iodide solutions were prepared in buffer solutions. One cc. quantities of the 2.4 per cent sodium iodide solutions were added to varying quantities of sterile F. D. A. broth and the pH effect noted. The buffering action in the pH range of 6.0 to 7.2 was identical in the 2.4 per cent sodium iodide solution as in the Iodine Solution (N. F. VIII) which consists of 2 per cent iodine and 2.4 per cent sodium iodide. This indicated that the buffering action of 2 per cent aqueous iodine may be attributed to the 2.4 per cent sodium iodide.

Color changes in 2 per cent iodine solutions started at pH 10.9 (10 cc. of N/1 sodium hydroxide + 100 cc. of 2 per cent iodine).

[3] The bromine solutions used in these tests were prepared by dissolving liquid bromine in the aqueous vehicle. No soluble bromide was present. These tests were repeated with a vehicle containing a soluble bromide, and identical results were obtained.

The color, usually considered the end point in the chemical preparation of sodium hypoiodite, was attained at pH 11.6 (15 cc. of N/1 sodium hydroxide + 100 cc. of 2 per cent iodine solution).

Summary and Conclusions

(1) Critical comparative tests for determining the bactericidal efficiencies of the free halogens under identical conditions were conducted with chlorine (as sodium hypochlorite), free bromine and free iodine against 24 hour-old cultures of *Staphylococcus aureus, Salmonella (Eberthella) typhosa, Escherichia coli, Pseudomonas aeruginosa, Bacillus mesentericus* (vegetative), *Bacillus megatherium* (vegetative) and *Bacillus subtilis* (vegetative).

Solutions containing available chlorine (2 per cent) were prepared from sodium hypochlorite 5 per cent. Free bromine solutions (2 per cent) were prepared by dissolving liquid bromine in water or by diluting Smith's Bromine Solution N. F. IV. Solutions containing free iodine were either Iodine Solution (2%) N. F. VIII or Iodine U. S. P. XIII Tincture (2%).

(2) Five cc. of the 2 per cent available chlorine prepared from sodium hypochlorite displayed bactericidal efficiency at 37°C. against 6 cc. of 24 hour-old cultures of *S. aureus* within 1 minute; 7 cc. of *S. aureus* in 3 minutes; 9 cc. of *S. aureus* in 5 minutes and 10 cc. of *S. aureus* in 15 minutes.

(3) One cc. of solutions containing 2 per cent available chlorine prepared from sodium hypochlorite was effective at 37°C. against 1cc. of 24 hour-old cultures of *S. aureus* in 1 minute, 2 cc. of *S. aureus* in 10 minutes and 3 cc. of *S. aureus* in 15 minutes.

(4) One cc. of solutions containing 2 per cent available chlorine prepared from sodium hypochlorite was effective at 37°C. against 15 cc. of 24 hour-old cultures of *S. (E.) typhosa, E. coli* and *P. aeruginosa* within 1 minute, but was ineffective against 1 cc. of 24 hour-old cultures of *B. mesentericus* (vegetative), *B. megatherium* (vegetative) and *B. subtilis* (vegetative).

(5) One cc. of Smith's bromine solution (21.8 per cent free bromine) was effective at 37°C. within 1 minute against 4 cc. of

24 hour-old cultures of *S. aureus*, within 10 minutes against 50 cc. of *S. aureus;* within 1 minute against 60 cc. of *S. (E.) typhosa;* 20 cc. *P. aeruginosa;* 60 cc. *E. coli;* 20 cc. *B. subtilis* (vegetative); 20 cc. *B. megatherium* (vegetative) and *B. mesentericus* (vegetative); and within 15 minutes against 30 cc. of 24 hour-old cultures of *B. megatherium* (vegetative) and *B. mesentericus* (vegetative). One cc. of Smith's bromine solution was ineffective against 1 cc. of 24 hour-old cultures of *B. subtilis* (vegetative) within 15 minutes at 37°C.

(6) Smith's bromine solution (21.8 per cent of free bromine) diluted to contain concentrations of free bromine 1:1000 (volume in volume) or less, in 5 cc. quantities was ineffective at 37°C. against 0.5 cc. of 24 hour-old cultures of *S. aureus, S. (E.) typhosa, P. aeruginosa, E. coli, B. mesentericus* (vegetative), *B. megatherium* (vegetative) and *B. subtilis* (vegetative) within 1 minute.

(7) One cc. of free bromine solution 1:1000 (weight in volume) was effective at 37°C. against 0.5 cc. *S. aureus, S. (E.) typhosa, E. coli* and *P. aeruginosa* within 1 minute at 37°C., but was ineffective against *B. mesentericus* (vegetative), *B. megatherium* (vegetative) and *B. subtilis* (vegetative) under the same conditions.

(8) One cc. of free bromine solution 1:4000 (volume in volume) in distilled water was effective against 0.5 cc. of 24 hour-old cultures of *S. aureus, S. (E.) typhosa, E. coli* and *P. aeruginosa* within 1 minute.

Free bromine solution 1:2000 (volume in volume) was effective against 5 cc. of 24 hour-old cultures of *B. subtilis* (vegetative), *B. megatherium* (vegetative) and *B. mesentericus* (vegetative) within 1 minute at 37°C.

(9) Two per cent free bromine (Smith's Bromine Solution diluted to 2 per cent free bromine concentrations with distilled water) in 1 cc. quantities was effective within 1 minute at 37°C. against the following amounts of 24 hour-old F. D. A. broth cultures: 3 cc. of *S. (E.) typhosa*, 3 cc. of *E. coli* and 1 cc. of *P. aeruginosa*. Two per cent free bromine solution in 1 cc. quantities was effective within 5 minutes against 1 cc. of *B. mesentericus* (vegetative). One cc. of 2 per cent bromine was not effective at

37°C. against 1 cc. of 24 hour-old cultures of *S. aureus, B. megatherium* (vegetative) or *B. subtilis* (vegetative) within 15 minutes.

(10) Two per cent free iodine solution was effective within 1 minute against the following amounts of 24 hour-old F. D. A. broth cultures: 20 cc. of *S. aureus, S. (E.) typhosa, E. coli* and *P. aeruginosa,* and 10 cc. of *B. mesentericus.*

(11) One cc. quantities of solutions containing 2 per cent chlorine (prepared from sodium hypochlorite solution) prepared in McIlvaine's buffer solution at pH 2.2, 3.0, 4.0, were capable of killing 5 cc. of 24 hour-old cultures of *S. aureus* at 37°C. within 1 minute at 37°C. One cc. of 2 per cent solution containing available chlorine prepared in McIlvaine's buffer solution at pH 5.0, 6.0, 7.0, and 8.0 was ineffective against 5 cc. of 24 hour-old cultures of *S. aureus* within 15 minutes at 37°C.

(12) Solutions of 2 per cent free bromine prepared in McIlvaine's buffer at pH 5.0, 6.0, 7.0, and 8.0 rapidly decomposed. One cc. of 2 per cent bromine solutions prepared in McIlvaine's buffer solutions at pH 2.2, 3.0, and 4.0 did not reveal bactericidal efficiency against one cc. of 24 hour-old F. D. A. broth cultures of *S. aureus* at 37°C.

(13) One cc. of 2 per cent iodine solutions prepared in McIlvaine's buffer solutions at pH 2.2 and 3.0 killed 25 cc. of 24 hour-old F. D. A. broth cultures of *S. aureus* within 1 minute at 37°C. Twenty cc. of 24 hour-old cultures of *S. aureus* were killed by one cc. of two per cent iodine at pH 4.0 and 5.0. Under the same method of testing 15 cc. of 24 hour-old cultures of *S. aureus* were killed at pH 6.0, 7.0 and 8.0 when prepared in McIlvaine's buffer or water adjusted with sodium hydroxide to alkaline pH ranges.

(14) One cc. of 2 per cent available chlorine prepared in McIlvaine's buffer solution did not display pH buffering action when in combination with sterile F. D. A. broth or 24 hour-old cultures of *S. aureus.*

(15) One cc. of 2 per cent bromine prepared in McIlvaine's buffer solution did not display pH buffering action when in combination with sterile F. D. A. broth or 24 hour-old cultures of *S. aureus.*

(16) One hundred cc. of 2 per cent bromine solution were titrated with normal sodium hydroxide to observe color change in relation to pH changes. The first color changes in the bromine-sodium hydroxide mixture occured at pH 7.4. The maximum color change occurred at pH 8.4.

(17) Two per cent iodine solutions prepared in water, 50° per cent alcohol, or McIlvaine's buffer solution displayed a buffering action against sterile F. D. A. broth and against 24 hour-old cultures of *S. aureus* within the pH range of 6.0 to 7.2. Sodium iodide, 2.4 per cent aqueous solutions, displayed buffering actions identical with that of the 2 per cent iodine solutions, which were prepared with 2.4 per cent sodium iodide.

(18) Slight color changes in 2 per cent iodine solutions occurred at pH 10.9 (10 cc. of N/1 solution of sodium hydroxide and 100 cc. of 2 per cent sodium iodide). The straw color usually considered the end point in the chemical preparation of sodium hypoiodite upon the addition of an excess of sodium hydroxide, was attained at pH 11.6 (15 cc. of N/1 sodium hydroxide and 100 cc. of 2 per cent iodine solution).

(19) From the findings reported above, it is evident that solutions containing free iodine, 2 per cent, displayed greater bactericidal efficiencies within one minute than was revealed by similar concentrations of free bromine or available chlorine under conditions of the technic used. Employing the same methods of testing, but adding McIlvaine's buffer solution, 2 per cent iodine solutions were more effective antibacterial agents within a very wide pH range than were displayed by similar concentrations of the other halogens.

(20) Bactericidal efficiency tests of the dilute halogens (1:5000) revealed that free iodine solutions displayed more effective antibacterial activity against the test bacteria than did chlorine or bromine at 37°C. or 24°C. either in the presence or in the absence of organic matter. Iodine solutions of such strength are suggested as being more effective for use as antiseptic washes or for irrigation purposes. Studies are being conducted to evaluate these halogens even in weaker concentrations, as found under conditions of use, when employed for swimming pools and for sanitization procedures.

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SCIENCE AND SCIENTISTS IN THE FEDERAL GOVERNMENT

By T. Swann Harding

THE government of the United States conducts or finances more than half of all the scientific research and development in the Nation. Its total expenditures for these rose from 345 million dollars in 1940, to well over 800 millions in 1945. Its expenditures for such purposes during 1947 exceeded 600 million dollars; private outlays during the same period totaled somewhat less than half this sum. Through contracts and other fiscal devices the government financed some 400 million dollars worth of industrial and university research annually.

For many years there has been a strong tendency for basic research to be performed by government, universities, or nonprofit foundations. That is because the profit motive is inimical to the pursuit of pure research, hence, by common consent, the private industries have tended to reserve that field to government, while they sought applications that would prove monetarily profitable. This was not wholly true, of course, because some enterprises were so wealthy and so vast that they could afford to finance some pure research.

By that very procedure they also became the sole owners and proprietors of huge pools of scientific knowledge their less wealthy competitors could not afford. They also tended to reserve for themselves the services of the most skilled practitioners of research. These factors gradually contributed to their power and actually became accessory to the increase of a monopolistic tendency in private business. It can therefore be quite advantageous for government to have taken over such a large sector of research, provided certain current practices are corrected.

Perhaps a definition is called for here. Pure, fundamental or basic research consists of theoretical analysis, exploration, or experimentation, often motivated by enlightened curiosity, with the broad objective of extending our knowledge of those general principles which govern natural and social phenomena. Background research, which is closely related thereto, is the systematic observation,

collection, organization, and presentation of facts, using known principles; its objective is clearly defined before the investigation is undertaken; it provdes a foundation for later research and also produces standard reference data.

During the past quarter century, those fields have more and more been left to government, the universities, and private foundations. Meanwhile industry has pursued applied research, its objective being specific practical applications, though it often involves the development of a specified novel product, process, technique or device. It has also carried on developmental research, which differs from applied, because its work is done on the improvement of already discovered or invented products, processes, techniques, or devices.

Our national expenditures for research and development, which increased 335 percent during World War II, are still three times as high as they were in prewar days. But the curtailment of education during the war has deprived the Nation of about half of its normal increase in scientists. Hence the drastic shortage of scientific personnel to round out the elaborate research programs now undertaken by government. Indeed the Department of Agriculture has found it all but impossible to procure scientists of the qualifications, kind, and number it requires to undertake the one hundred and fifty odd new projects approved under the Research and Marketing Act of 1946.

The scientific progress of the United States depends upon about one-half of 1 percent of its population—say three quarters of a million persons. Within this pool is a much smaller group of 137,000 individuals comprising the scientists and engineers actually engaged in research and technical development or in teaching, in colleges and universities, industry, and government service. A still smaller group of about 25,000 of these have doctor's degrees in physical, biological, or agricultural sciences.

In 1937, the federal government employed about 14,000 scientists; this figure rose to 35,000 by 1945, but has fallen to about 30,000 today. Industry, in 1937, employed about 22,000 scientists, a figure which rose to 57,000 in 1945, and remains there today. Our colleges and universities, in both 1937 and 1945, employed about 36,000 scientists, but the figure is now 50,000 largely because they are carrying out so many government-subsidized projects.

More specifically, the government's present expenditures for research and development in the physical and biological sciences amounted to about 625 million dollars in the fiscal year 1947. This figure includes the expenditures of the Atomic Energy Commission and of those agencies which have had no significant allocation of funds for research. Of this sum 80 percent is expended by the War and Navy Departments, hence the military program absorbs five-sixths of the total federal funds.

However, we must remember that the line is not clear between military and nonmilitary research and development. It blurs. Research by the Civil Aeronautics Administration on passenger and cargo planes often starts from military findings. The National Advisory Committee for Aeronautics engages in background investigations applicable to either civilian or military craft. The biological investigation to develop a fungus-resistant tomato variety led to the discovery of tomatin, an antibiotic which, on analysis, yielded substances capable of counteracting ringworm among those who wore military footwear.

Moreover, the great bulk of the government's funds are expended on applied and developmental research, say 570 of the total 625 million dollars. The armed services so expend 465 million dollars of the 500 they receive. Of the 100 million dollars allocated to the four largest civilian research establishments—Agriculture, Commerce, Interior, and the National Advisory Committee for Aeronautics—only about 85 millions go for basic research, and most of that to background, not to fundamental.

Less than 6 percent of the government's research funds go to support investigations in all its other agencies not named above. These include the following: Department of the Treasury, Federal Loan Agency, Federal Works Agency, Smithsonian Institution, Tennessee Valley Authority, Department of Justice, Federal Communications Commission, Federal Power Commission, U. S. Maritime Commission, Public Health Service, Food and Drug Administration, and Veteran's Administration.

About a third of the federal money spent for research and development finances work within its own laboratories. Nearly all of the civilian research is so carried on, though the following contract all or a good portion of their projects: Office of Rubber Reserve, Office of Technical Services, Commerce Department, and Civil

Aeronautics Administration. The primary users of contract research are the Army and Navy which pay out four-fifths of their funds to universities and industries which conduct the investigations, the former doing the basic and background and the latter the developmental work. In addition, about half the hundred millions used for military research not covered in contracts was transfered to other civilian agencies in government.

So far it appears that there is a real dearth of qualified manpower, that the government does proportionately too little fundamental research, and that the great preponderance of the government's funds go to investigations that have potential military significance or value. The government carries on its research in hundreds of installations scattered through the country and operating under fifty-odd more or less independent bureaus located within its major agencies.

The Department of Agriculture alone has nearly 200 installations here and abroad, some employing only two or three scientists, some a hundred or more. It is by all odds the main civilian research agency of the federal government in scope of program, personnel involved, dispersion of field forces. It maintains complicated relationships to the state experiment stations which, in 1947, received a total of $7,206,208 of federal grant funds, though they also expended 26 million dollars of non-federal funds during the same fiscal year.

Many minor federal research programs no doubt escape our notice altogether, yet they must be considered if we are to have an accurate picture of what goes on in government science. The Bureau of Engraving and Printing has a research laboratory which, during the past decade, has accumulated savings of $12 millions, much of it being passed along to the agencies it serves. It developed such things as new electronically controlled postage-stamp perforating machines and currency platering processes, ink formulae, multicolor presses, and more economical techniques of handling war bonds.

The Bureau of the Mint performs metallurgic research of a highly complex character. The Coast Guard must allocate money for research to keep it informed regarding technical progress and to increase the efficiency of its operations. The four main research bureaus of Interior are the Geological Survey, Bureau of Mines, Fish and Wildlife Service, and the Bureau of Reclamation. The

National Bureau of Standards is best known to the public in Commerce, but the Office of Technical Services, Civil Aeronautics Administration, Weather Bureau, Coast and Geodetic Survey, and even the Bureau of the Census all have research programs.

The Department of Agriculture and the state experiment stations carry on a well-coordinated program which covers the physical, biological and social sciences. The Department's research is primarily performed in the Agricultural Research Administration, consisting of seven specialized bureaus, the Production and Marketing Administration, Forest Service, Soil Conservation Service, Farm Credit Administration, and Bureau of Agricultural Economics. The program costs less than 32 million dollars annually, about 5 percent of the government's total expenditures and estimated returns to the American public on the investment vary from 500 to 10,000 percent.

Oddly enough the Nation as a whole invests only about 110 million dollars annually in scientific research and development in medical and allied fields. In 1947, the federal government's expenditures in this field were 28 million dollars, or approximately 4 percent of its total allocated to research and development. Before the war the amount expended was much less, but federal medical research is still hampered by shortage of manpower and funds, and imbalance between types of research. There is still too little basic research in this field, and we lack a national policy for medical research as well.

Experts believe that the federal government should expend 300 million dollars annually on medical research. Its program is now carried on primarily in the Public Health Service, with its Hygienic Laboratory founded in 1887, the Veteran's Administration, the Food and Drug Administration, and the military establishments. However, research in the Department of Agriculture, particularly that in its Bureau of Animal Industry, tends to get into the human medical field. The same is true of investigations it carries on upon drug plants, insect control, antibiotics, and its surveys of the status of rural medical care.

The total effect of World War II on scientific personnel has not yet been fully felt. The curtailment of educational opportunity and the drafting of students together deprived us of about 90,000 with a bachelor's degree and 5,000 with a doctor's degree, figures

that will rise to 100,000 and 8,400, respectively, before the effects of war-reduced educational enrollments are overcome. Since only about 90 percent of the doctors and a third of the bachelors normally enter teaching or research, the net loss is probably more nearly 40,000, insofar as these activities are concerned.

What is the position of those 30,000 scientists in government service? Since the earliest surveys made, the prestige of holding a government job has ranked very low. In our culture, with its heavy emphasis on private initiative, government is traditionally mistrusted and habitually misjudged. Only about 37 percent of the 30,000 regard government employment as productive of the greatest career satisfaction, this in spite of the fact that some of the most outstanding scientific discoveries have been made by federal scientists.

Scientists as a whole tend to look upon university work most favorably. Yet it is quite as possible for a worker to become boxed in, trapped in a blind alley, deprived of advancement, in a university as in the government service, while all these and other difficulties, including that of being placed under a non-scientifically trained administrator, face the scientist in industry. The position of scientists in government is better than hostile critics contend but not so good as it might be. Their environment is such that they can perform research of top quality (See *Two Blades of Grass*, University of Oklahoma Press, for proof).

Federal employment has some very definite advantages that are often overlooked by those who pretend to deplore the horrors of such work. Among these are nominal job security—periodically disturbed by arbitrary cuts in appropriations and personnel and loyalty jitters—vacations and sick leave with pay, regular increases in salary, and well-established and quite liberal retirement benefits.

Moreover, the physical facilities for research throughout government vary from good to lavish. Adequate funds for the operation of research programs are normally made available. Except in national emergencies, federal scientists do not work under pressure or on rigid time schedules and, naturally, the more or less immediate monetary profits required by private industry do not have to be considered. There is considerable freedom in choice of problems, and the program is so varied that almost any kind of specialized

expert can find something to interest him somewhere. Many federal scientists work exclusively on self-selected projects.

Moreover federal scientists have as much freedom as university scientists and probably more; they certainly have no less than the average research worker in private industry. The pay offered to younger scientists is usually better than that given persons of comparable training and experience by colleges and universities. But the $10,000 ceiling makes it difficult to hold investigators and research administrators of exceptional ability. They can and they usually do find industrial earnings far superior.

Federal government recruitment, promotion, and dismissal procedures leave little to be desired and certainly compare favorably with those elsewhere. The loyalty tests are prying in nature, but one hopes they represent a mere temporary hysteria. Moreover, at least in Agriculture, there is now in effect a system of presenting Distinguished and Superior Service Awards to employees, which are often won by research workers, while scientists also profit by meritorious promotions for superior accomplishments. The above-mentioned awards consist of appropriate medals and certificates.

On the other hand there are disadvantages in federal employment, over and above those incidental to sporadic and sudden curtailment of projects or personnel. The government is miserly in the matter of travel funds, mainly on the theory that any trip of any kind must be a secret recreational adventure. It is difficult enough for federal scientists to get their way paid to meetings of their own professional societies, particularly if they do not themselves give a paper. In fact the tendency is strong to cook up a paper just to get to the meeting.

It is still more difficult for the federal research worker to visit his colleagues at their own laboratories, a procedure that is stimulating and fructifying, and that often saves the visiting scientist much expensive, time-wasting labor in his laboratory. He may do work as interesting and certainly as valuable as he would do anywhere, but funds for visiting his colleagues are almost impossible to get, while sabbatical leave is quite unknown. If he wishes, the federal scientist can sometimes arrange for extended leave without pay, but few of them can afford such extravagance.

While the results of the scientist's investigations undergo no such censorship and close scrutiny in government as they do in in-

dustry, there is such a thing as security. Some scientists demur, but the present state of the world makes this unavoidable. On the other hand, many university scientists cannot publish certain of their findings for fear of offending specific individuals of wealth or powerful groups. However, there are always severe limitations on the funds available for the publication of scientific work by federal government research units.

This has gone on for years. Many federal scientists prefer to publish in the outside journals of their professional societies in order to reach a larger audience. But many have to publish outside or face all but interminable delays in the effort to publish at government expense. The fact has never been faced clearly that a definite percentage of the funds appropriated for research should be allocated to its publication. So, for years, various government agencies have had to hold unpublished many manuscripts recording the results of valuable research, for which the public paid.

It is somewhat difficult to arrange civil service examinations for prospective scientific workers in government, but progress is being made here. Selection also offers difficulties, for not just any specialist who can pass an examination will fit into the particular niches to be filled. Next the ordinary type of efficiency ratings apply poorly to work so exploratory and so highly personalized as scientific research.

But the government scientist has a relatively good opportunity for growth and advancement. His supervisor, at least in the civilian establishments, is generally qualified technically. He can obtain freedom from nonscientific work at a fair salary, if he strongly desires, by avoiding administrative duties. Future prospects for science and scientists in government look brighter.

It is unlikely that federal funds for research will ever revert to the prewar level. Advances are being made in the allocation of project funds for periods longer than the customary single fiscal year. New techniques for the recruitment, examination, appointment, and advancement of qualified scientific personnel are in the making. There is a strong and growing opinion favorable to legislation permitting the payment of salaries as high as $15,000 a year to those who fill top-flight scientific positions.

Merit is constantly being better recognized; the prestige of government research rose enormously during the war. Scientific

administration for scientific workers is becoming the rule. Efforts are being made to procure funds to finance sabbatical leave with pay for top-grade government scientists, as well as for more frequent attendance at professional meetings and visits to distant colleagues. Finally, more adequate funds must soon be provided for the quicker publication and wider dissemination of research results, or the situation will become intolerably stupid and ludicrous.

Science and scientists in government are on the way to better things. But they never were as bad off as many ill-informed critics have claimed.

SELECTED ABSTRACTS

Penicillin Tablets in the Prophylaxis of Gonorrhea. H. Eagle, A. V. Gude, G. E. Beckmann, G. Mast, J. J. Sapero, and J. B. Shindledecker. *Public Health Reports 63:*1411 (1948). A preliminary report by the authors discusses the results of a study to test the possibility that penicillin tablets taken a few hours after exposure would prevent the development of gonorrhea. The study was performed on a group of 350 naval personnel. The men were divided into two equal groups. One received a peroral tablet containing 100,000 units of penicillin immediately upon return from liberty and the other group received a placebo. Following a period of 24 weeks it was found that the controls had had 3,616 liberties with 43 cases of gonorrhea. The incidence was thus 11.9 cases per 1,000 liberties or 508 cases per 1,000 men per year. The treated group, during 16 weeks, had had 3,218 liberties with 5 cases of gonorrhea, in 3 of which there was doubt that they had received the penicillin tablet. The incidence was thus 1.8 cases per 1,000 liberties or 105 cases per 1,000 men per year. During the last 8 weeks of the study the dose for the treated group was increased to 250,000 units of penicillin. During this period there were 569 liberties and only 1 case of gonorrhea with doubt that this person had received the penicillin.

Following this study the men were placed on a voluntary basis relative to the penicillin. A 250,000 unit tablet was available for each man following liberty if he wanted it. During an 8 week period there were 1,943 liberties with a request for prophylaxis following 670 liberties. During this period 7 cases of gonorrhea developed but 6 and possibly all 7 of them were in men who had not elected to receive the penicillin tablet.

The study did not attempt to determine the length of time after exposure in which a single 250,000 unit tablet of penicillin would be reasonably effective. During the study there was no evidence of sensitization to penicillin, no apparent development of penicillin-fast strains of gonococcus, and no instance of suppressed syphilitic infection. The average intake of penicillin was 1.1 tablets per week for the entire group.

Effect of Hyaluronidase and Hyaluronic Acid on Cultures of Flagellates. H. Seneca, E. Henderson, and M. Harvey. *Science 108:*714 (1948). The complex polysaccharide, hyaluronic acid, and its specific enzyme, hyaluronidase, were studied *in vitro* to determine their effect upon *Leishmania donovani, Trypanosoma cruzi,* and *Endamoeba histolytica.*

Following culture the organisms were suspended in normal saline containing varying strengths of the test substances and also subcultured in the presence of the test substances.

In the presence of hyaluronidase *L. donovani* and *T. cruzi* showed no change in the rate of multiplication, vitality nor motility as compared with control preparations. *E. histolytica* showed a hypermotility but no change in vitality nor structure in suspensions but showed an enhancement of growth after serial transplantations.

In the presence of hyaluronic acid the hemoflagellates showed a reduction in motility in 0.5 per cent suspensions but with no evidence that the organisms were killed. Otherwise no effect was noted on these organisms. *E. histolytica* showed complete degeneration within 15 min. in an 0.5 per cent suspension. Culture transplants of the amoebae resulted in death in the 3rd generation in the presence of 5 mg. of hyaluronic acid per 5 cc.

These results suggest that hyaluronic acid may be useful therapeutically by acting directly against *E. histolytica* and also by inhibiting hyaluronidase and thus possibly reducing the ability of the organism to invade the tissues of its host.

Hexachlorocyclohexane, A New Potent Scabicide. A. B. Cannon and M. E. McRae. *J. A. M. A. 138:*557 (1948). For many years sulfur was the treatment of choice for scabies. Other preparations were used but none stood the test of time as did sulfur in the form of an ointment. However, the treatment was very messy and the advent of benzyl benzoate and DDT lotions did much to remedy this aspect as well as improve the results. However, these latter preparations frequently caused irritation and sensitivity. The gamma isomer of 1, 2, 3, 4, 5, 6-hexachlorocyclohexane seems to promise improvement over all of these preparations in that it is highly effective and virtually nontoxic and nonirritant.

The authors report the use of 1 per cent 1, 2, 3, 4, 5, 6-hexachlorocyclohexane in a vanishing cream base. The cream was used on 100 unselected cases of proven scabies with 100 per cent cure. Of this group 61 required but one treatment, 36 but two, and 3 required three treatments. Complete relief from puritis was obtained within 24 to 48 hours and many observed that itching ceased within 2 or 3 hours.

The treatment consisted of covering the entire cutaneous surface with a thin film of the cream. About 15 to 25 Gm. were required for one adult treatment. After 24 hours a thorough bath was taken and all underclothing, night clothes, and bed linen were changed and washed. The patient was examined after one week in order to give ample time for any ova to hatch.

This remedy was found to be effective even in cases where other remedies had failed. There were no indications of irritation even in the presence of severe dermatitis from scratching. Toxicity tests on animals revealed low toxicity when applied to the skin or when administered orally.

This drug has also proven to be effective in the control of chiggers, ticks, fleas, cockroaches, bedbugs, and pediculosis capitis, corporis and pubis.

Patch tests for the determination of sensitivity development were performed one to two months after cure on 34 patients. None showed evidence of the development of sensitivity to hexachlorocyclohexane.

Successful Treatment of Brucellosis With Sulfadiazine and Streptomycin. E. F. Scowen and L. P. Garrod. *Brit. Med. J. No. 4590:*1099 (1948). The causative agent of brucellosis, *Brucella abortus*, has been shown to be sensitive both to sulfadiazine and to streptomycin. However, treatment with either of these drugs alone has brought only disappointing results. Since two chemotherapeutic agents of partial effectiveness may be additive or synergistic when employed together, trials have been made combining these two agents. Reports have varied, some workers reporting success and some failure with this combined therapy.

The authors report the results of combined therapy in two cases of proven undulant fever, one in the early stages and the other in

later stages. The therapy employed was 2 Gm. of sulfadiazine by mouth every 4 hours for 3 doses each day and 1 Gm. of streptomycin intramuscularly every 8 hours for 3 doses each day. This regimen was continued for 14 days. The patient having late stage brucellosis responded with a drop in temperature to normal within 3 days and the other patient showed a return of temperature to normal by the end of the course. At the time of the report the patients had been afebrile and 2 months respectively.

The authors suggest that the successful results from therapy in these two cases may be due to the larger daily doses of the two chemotherapeutic agents, as compared with previous reports in which failures had been recorded.

Toxic Reactions During Streptomycin and Sulfadiazine Therapy of Brucellosis. N. B. McCullough and C. W. Eisele. *J. A. M. A. 139:*80 (Jan. 8, 1949). Streptomycin has been shown to produce toxic effects on the eighth cranial nerve and a few instances of other neurologic involvement have been reported. During the course of treatment of brucellosis with combined therapy of streptomycin and sulfadiazine the authors pointed out that they had encountered toxic reactions to the nervous system which seemed to be out of proportion to the small doses of streptomycin given and to involve more widespread areas of the brain than had previously been recognized. A common occurrence among the patients receiving combined therapy was circumoral paresthesia accompained by demonstrable hypalgesia. These symptoms usually developed within a few days after therapy was started.

Two cases were described by the authors in which severe encephalopathies were encountered within a few hours after the initial dose of streptomycin.

The authors pointed out that the minor clinical signs such as the paresthesias, which commonly accompany streptomycin therapy, should not be disregarded. They also pointed out that the frequency and severity of the toxic effects on the nervous system which they had encountered in the combined therapy of brucellosis suggests that this combination increases the toxicity as well as the effectiveness of streptomycin or that the nature of the disease increases the hazards.

Bacteriological Properties of a New Antibiotic, Circulin. Charlotte McLeod. *J. Bact. 56:*749 (1948). Circulin is an antibiotic obtained from broth cultures of a mucoid variant of *Bacillus circulans.* It is polypeptide in nature and has been obtained in crystalline form. It is bactericidal as well as bacteriostatic against gram-positive and gram-negative bacteria and against numerous fungi.

Potency of the substance is measured by assaying dilutions against broth cultures of the test organism. A unit of activity has been defined as the minimum amount of active substance that will completely inhibit the growth of *Escherichia coli* in 1 cc. of nutrient broth for 24 hours. In the assay system as much as 25 per cent of blood serum has no appreciable effect on the activity of circulin.

However, circulin is hemolytic and very toxic. The LD_{50} for mice is 0.3 mg. by intraperitoneal injection. These characteristics make the antibiotic unsuitable for parenteral therapy, but limited trials indicate that it may have value in the treatment of bacterial and fungal infections of the skin.

It was found that crystalline preparations in solution in dilute hydrochloric acid may be stored for a period of at least 2 years at 4°C. without loss of activity. The antibiotic is filterable through a Zeitz filter without loss of activity.

The author points out that further attempts will be made to reduce the toxicity of this antibiotic.

Methylcellulose Found to Be Good Laxative. Karl Schweig. *N. Y. State J. Med. 48:*1822 (1948). Another use for the synthetic hydrophilic colloid methylcellulose has been found in the relief of chronic or acute constipation. The author reports in the passage of normal, soft, bulky stools without accompanying griping, cramping, or tenesmus in most of 37 cases following the administration of tablets of methylcellulose. The patients received the colloid for periods from 3 to 240 days without showing any systemic changes or indications of toxicity. There was also no gastrointestinal upset.

Since methylcellulose forms a colloidal solution in any given amount of water there is practically no danger of impaction, which is occasionally encountered with natural gums. The degree of

viscosity of the colloidal solution varies from a soft, smooth gel to a thin liquid depending on the amount of water available. Another advantage of the synthetic colloid over natural gums is to be found in its chemical uniformity.

Aureomycin Therapy in Human Brucellosis. W. W. Spink, A. I. Braude, M. R. Castaneda, and R. A. Goytia. *J. A. M. A. 138*:1145 (1948). Plans were made to treat a group of patients in Mexico with the malignant form of brucellosis caused by *Brucella melitensis*. Treatment was to consist of intramuscular injections of streptomycin every 6 hours for 2 weeks in a dose of 0.5 Gm. Simultaneously sulfadiazine was to be given orally in a dose of 1 Gm. initially and then 1 Gm. 3 times a day for 2 weeks. After several patients had been treated with this program the incidence of vestibular function, disappointing clinical results, and the very great shortage of beds led to the substitution of aureomycin for streptomycin. *In vitro* and infected chick embryo experiments had shown aureomycin to be active against *Br. melitensis* but less so than streptomycin, weight for weight. However, aureomycin could be administered orally and thus the patients could be ambulatory. The clinical results far surpassed expectations.

All patients were proven to have infections due to *Br. melitensis* by blood cultures before therapy was begun. Aureomycin alone was found to give very encouraging results. The authors emphasized, however, that their report was only relative to the immediate therapeutic effects from treatment with aureomycin and that in a disease such as brucellosis it is essential that there be a long follow-up period in order to evaluate the drug completely.

The recommended dosage of aureomycin was 0.1 Gm. in 4 divided doses the first day, 0.6 Gm. the second day, 1.6 Gm. the third day, add 2 Gm. the fourth day and each succeeding day until the drug had been given for 10 days. This regimen was followed because it was found that if large doses were given initially there was a febrile reaction associated with a drop in blood pressure.

An addendum appended to the original article reported that of 24 patients treated 3 patients had shown positive blood cultures following therapy. Therefore the authors recommended that the total daily dose be increased from 2 Gm. to 4 to 6 Gm. for 2 weeks.

BOOK REVIEW

Dermatology and Venereology for Nurses. By John H. Stokes, M. D., and Jane B. Taylor, B. S., R. N., Fourth Edition, 416 pages, 1948. W. B. Saunders Co., Philadelphia. Price $.

This is an excellent descriptive and illustrated text concerned with the diagnosis, management and treatment of diseases of the skin and venereal diseases. The book was written to provide a comprehensive public health and sociological background for nurses. Included are tables and schedules of the basic principles and technics to be carried out by nurses under medical supervision.

The first half of the book, Part I, deals with a descriptive summary of diseases of the skin. Part II deals with the nursing problems and responsibilities with treatment of cutaneous disease, discussing general principles, the types and uses of local applications and internal medication. The remainder of the book, Parts III and IV, deals with the venereal diseases and the principles of social hygiene. An appendix is included as a reference for those interested in further information. This is followed by a glossary of medical terms.

The book written at a high professional level, should prove most useful to the pharmacist as a "thumb nail" reference for the principles of modern diagnostic procedures and treatment in dermatology and the venereal diseases.

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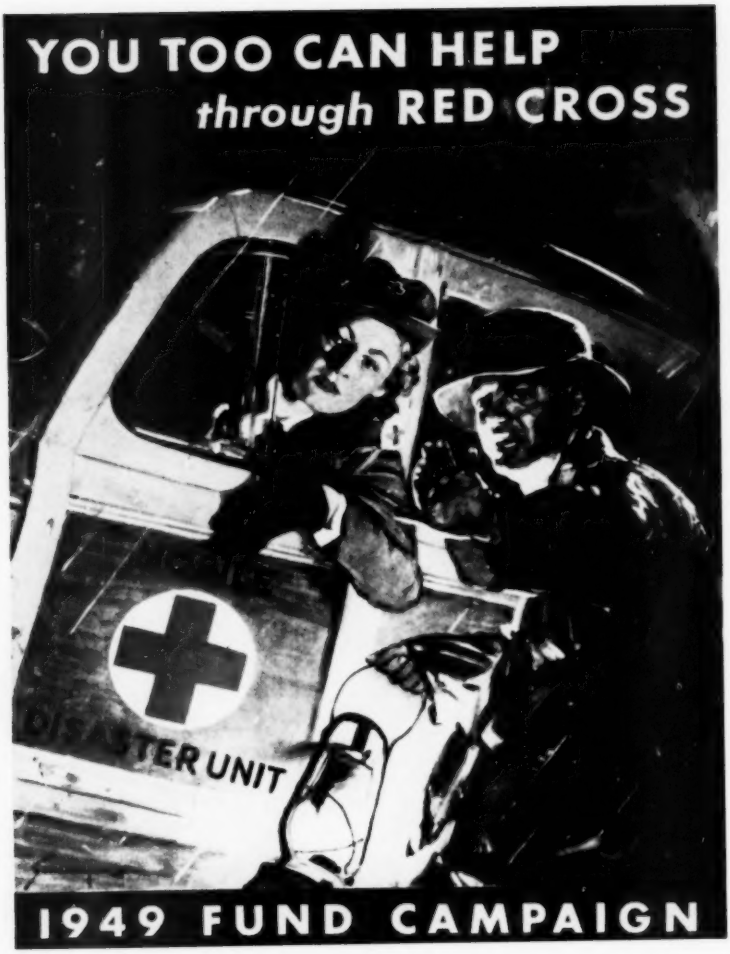
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